REMARKS

1. Preliminary Remarks

a. Status of the Claims

Claims 29, 30 , 32, 35, 36, 38, 41, 42, 44, 62, and 63 are pending and under active consideration in this application. Applicant respectfully requests entry of the remarks made herein into the file history of the application.

2. Patentability Remarks

a. 35 U.S.C. § 103

At items 3-8 of the Office Action, the Examiner rejects claims 29, 30, 32, 35, 36, 38, 41, 42, 44, 62, and 63 under 35 U.S.C. § 103(a) as allegedly being unpatentable over U.S. Patent No. 5,260,305 ("Dennick" hereafter) in view of either Saito *et al.* (Arteriosclerosis and Thrombosis, 1991;11:816-26; "Saito" hereafter) or U.S. Patent No. 5,116,610 ("Broaddus" hereafter) and Saito. The Examiner asserts that Dennick discloses the following: (1) using a combination of cholesterol-lowering drugs including niacin to lower cholesterol levels ; (2) using a dose of niacin as high as 2000 mg in a single or divided dosage form[1]; (3) the swellable polymers of gelatin and starch; and (4) a 1500 mg dose of niacin, since Dennick teaches starting with a low dose and working to a high dose of up to 2000 mg. According to the Examiner, the only instant limitation Dennick fails to teach is administering the cholesterol-lowering drugs at night. The Examiner alleges that Broaddus discloses night administration of a cholesterol-lowering composition including cholestyramine and polyol esters, and that Saito discloses that the cholesterol-lowering drug simvastatin is more effective when administered once per day in the evening as compared to the morning. The Examiner concludes from the cited references that it would have been obvious to one of ordinary skill in the art to administer the niacin composition of Dennick at evening or at night, since Broaddus and Saito suggest administering cholesterol-lowering substances at these times is safe and effective. The Examiner also asserts that one of ordinary skill in the art based on these references would have expected that administering cholesterol-lowering substances in this way would not have any associated side effects such as hepatotoxicity. Applicant respectfully disagrees.

The rationale for the Examiner's rejection is that there was some motivation in the prior art that would have led one of ordinary skill to combine prior art reference teachings to arrive at the

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[1] It is actually a range of 2-3000 mg. *See* Dennick at column 3, lines 61-63.

claimed invention. *See* MPEP § 2143.G. Applicant submits that no such motivation exists. The instantly claimed method relates to achieving balanced lipid alteration in a patient using an **intermediate release formulation** of nicotinic acid that has a **specific dissolution profile**. Applicant submits that the claimed subject matter is not obvious over the cited references because the cited references fail to indicate that one of ordinary skill in the art would have any motivation to arrive at an intermediate release formulation of nicotinic acid with the claimed dissolution profile, and provide no expectation of success that the claimed formulation would be free of hepatotoxic effects. *See* MPEP § 2143.

Dennick fails to disclose a intermediate release formulation of nicotinic acid, and provides no motivation to one of ordinary skill in the art to arrive at one. Instead, this reference teaches only an extended release version. *See* Dennick at column 6, lines 35-40 ("[patients] were randomized to 8 weeks of treatment of [double-blind placebo], [pravastatin sodium 40 mg] at bedtime, **NA [nicotinic acid] 1 g [twice a day] (as extended release capsules)**…")(emphasis added). Dennick further fails to recognize that use of extended (i.e., sustained) release formulations of nicotinic acid results in greater incidences of liver toxicity. *See* J.M. McKenney, JAMA, 1994;271(9):762-7 at abstract ("McKenney" hereafter)("[t]he SR [sustained release] form of niacin is hepatotoxic and should be restricted from use") *and* Instant Application at page 3, line 13-page 4, line 22 ("… SR nicotinic acid formulations have been noted as causing greater incidences of liver toxicity"). This is one of the main problems that the instant subject matter is intended to solve. *See* Instant Application at page 1, lines 11-13 ("Specifically, the present invention employs a composition of nicotinic acid… to treat hyperlipidemia in a once per day oral dosage form given during the evening hours that causes little if any hepatotoxicity").

Specifically, the instantly claimed treatment method avoids the hepatotoxicity associated with sustained release nicotinic acid by requiring that about 40-60% of nicotinic acid be released from the claimed formulation after about 9 hours. *See* Instant Application at page 7, lines 12-17. The instantly claimed nicotinic acid dissolution profile is different from sustained release formulations. *See* Instant Application at page 14, lines 17-24 ("… the nicotinic acid formulations of the present invention are responsible for a controlled absorption profile that is intermediate to that of [intermediate release] and [sustained release] nicotinic acid formulations currently commercially available"). Because Dennick fails to disclose that sustained or extended release nicotinic acid formulations are hepatotoxic, and in fact teaches the desirability of using a sustained release formulation, one of ordinary skill in the art would not have been motivated to arrive at the instantly

claimed subject matter, including the specifically claimed nicotinic acid dissolution profile. Neither Broaddus nor Saito remedies the severe deficiencies of Dennick, particularly because their teachings have nothing to do with nicotinic acid, and rather only focus on the timing administration of **other**, unrelated cholesterol-lowering substances.

Additionally, none of the cited references provides any expectation to one of ordinary skill that an intermediate release formulation of nicotinic acid could have a favorable safety profile. As discussed above, Dennick teaches no extended release nicotinic acid formulations and focuses solely on the desirability of sustained release nicotinic acid, despite the fact that it is hepatotoxic. Additionally, the teachings of Broaddus and Saito are completely irrelevant as to whether any particular nicotinic acid formulation could be made safe–namely because these references are about **completely different drugs**. As admitted by the Examiner at items 6 and 7 of the Office Action, Broaddus discloses using cholestyramine and polyol esters for reducing cholesterol levels, while Saito discloses using simvastatin. The safety profiles of these cholesterol-reducing substances **have absolutely no relation to the safety of nicotinic acid formulations**. One of ordinary skill in the art recognizes that each substance has its own safety profile, and that one cannot have any expectation as to whether a particular substance will be safe until it is actually tested. Thus, the Examiner's contention that the cited references suggest that administering nicotinic acid at evening or bed time is "safe and effective," and that balanced cholesterol level reduction could be achieved, "without any associated side effects such as hepatotoxicity," is simply incorrect. The instant application, however, does disclose that the instantly claimed nicotinic acid formulation shows no detectable liver toxicity. In particular, Table VIII and page 44, lines 1-7 indicate that in a clinical trial testing the claimed dosage form, no patients dropped out because of an increase in liver function tests, and it caused no liver damage. There would have been no way for one of ordinary skill to have expected these results based on any of the teachings of the cited references. Accordingly, the cited references provide no motivation or expectation of success for one of ordinary skill to arrive at the instantly claimed subject matter. In view of the foregoing remarks, Applicant respectfully requests that the Examiner reconsider and withdraw the claim rejections under 35 U.S.C. § 103.

3. Conclusion

Applicant respectfully submits that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite the prosecution of the instant application, the Examiner is encouraged to call the undersigned at the number listed below.

Respectfully submitted,

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